One-pot, four-component synthesis of new 3,4,7,8-tetrahydro-3,3-dimethyl-11-aryl-2*H*-pyridazino[1,2-*a*]indazole-1,6,9(11*H*)-triones and 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-triones using an acidic ionic liquid *N,N*-diethyl-*N*-sulfoethanammonium chloride ($[Et_3N–SO_3H]Cl$) as a highly efficient and recyclable catalyst

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Graphical Abstract

One-pot, four-component synthesis of new 3,4,7,8-tetrahydro-3,3-dimethyl-11-aryl-*2H*-pyridazino[1,2-*a*]indazole-1,6,9(11*H*)-triones and 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-triones using an acidic ionic liquid *N*,*N*-diethyl-*N*-sulfoethanammonium chloride ([$Et_3N–SO_3H$]Cl) as a highly efficient and recyclable catalyst

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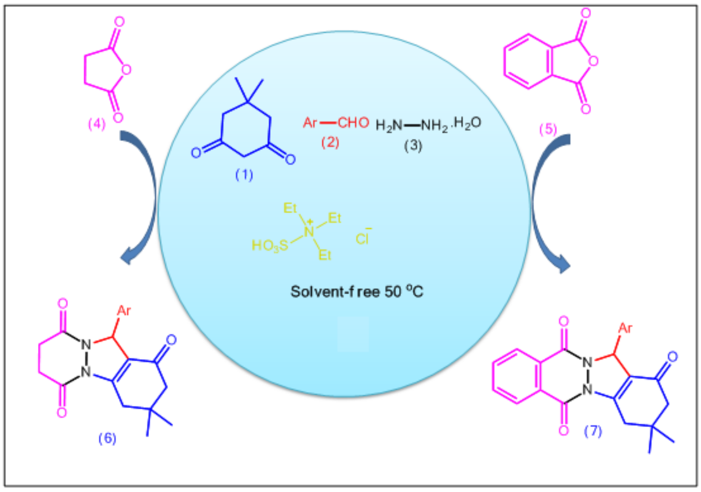

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ABSTRACT

A rapid and efficient one-pot, four-component protocol for the synthesis of novel 2*H*-pyridazino[1,2-*a*]indazole-1,6,9(11*H*)-triones **(6)** and 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11-triones (**7**) has been developed using a stable and reusable Brønsted acidic ionic liquid *N,N*-diethyl-*N*-sulfoethanammonium chloride ([$Et_3N–SO_3H$]Cl). A range of diverse aldehydes were successfully applied and the corresponding products obtained in good to excellent yields without any by-products.

1. Introduction

Multi-component reactions (MCRs) play an important role in organic and medicinal chemistry because of their ability to synthesize target compounds with high efficiency and atom economy by generating structural complexity in a single step from three or more reactants. Moreover, MCRs offer the advantage of simplicity and synthetic efficiency over conventional chemical reactions.[1] Therefore, the design of these reactions for the synthesis of diverse groups of compounds, especially those that are biologically active, have gained great attention in organic synthesis.[2-4]

Recently, the use of ionic liquids (ILs) as green solvents has found versatile applications in organic reactions due to their promising features such as the ability to control product distribution,[5] enhanced rate[6] and/or reactivity,[7] ease of product recovery,[8] catalyst immobilization,[9] and recycling.[10] Ionic liquids have also been effectively utilized for the synthesis of novel bioactive compounds.[11]

Among heterocyclic compounds, great focus has been directed towards bridgehead nitrogen-containing heterocycles especially those containing the hydrazine group such as pyridazine since they possess pharmacological and biological activities such as herbicides, insecticides and fungicides.[12-14]

Indazole [2,1-*b*]phthalazine-trione are another category of bridgehead hydrazine-containing heterocycles which are bioisosteres of indoles and have been widely used in medicinal chemistry.[15] In fact, compounds containing the indazole moiety are known to show a variety of biological activities, such as high binding affinity for the estrogen receptor,[16] inhibition of protein kinase C-β,[17] 5-HT2 and 5-HT3 receptor antagonism,[18] human immunodeficiency virus (HIV) protease inhibition,[19] and anti-tumor activity.[20] Different catalysts such as supported polyphosphoric acid,[21] dodecylphosphonic acid,[22] $Ce(SO_4)_2$,[23] modified PEG-6000,[24] heteropolyacids,[25] trimethylsilyl chloride,[26] $Mg(HSO_4)_2$,[27] and cyanuric chloride[28] have been reported for the preparation of these compounds.

A recent protocol directed toward the design of structural motifs containing the pyridazino[1,2-*a*]indazole ring fragment by condensation of aldehydes and dimedone followed by the reaction with 2,3-dihydro-1,4-1,2-dihydropyridazine-3,6-dione has been reported.[29]

In a continuation of our research on ionic liquids and their application as catalysts in organic synthesis,[30] we have investigated the one-pot, four-component synthesis of new derivatives of 3,4,7,8-tetrahydro-3,3-dimethyl-11-aryl-2*H*-pyridazino[1,2-*a*]indazole-1,6,9(11*H*)-trione and known derivatives of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11-trione using *N,N*-diethyl-*N*-sulfoethanammonium chloride ([$Et_3N–SO_3H$]Cl) as a highly efficient and recyclable catalyst under solvent-free conditions. The ionic liquid was prepared according to the reported literature procedure.[31]

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2. Results and Discussion

Firstly, the four-component reaction of benzaldehyde **(2a)** (1 mmol), dimedone **(1)** (1 mmol), hydrazine hydrate **(3)** (1.2 mmol) and succinic anhydride **(4)** (1 mmol) was chosen as the model reaction and examined in the presence of various ionic liquids and Brønsted acid heterogeneous catalysts under different conditions. In the absence of catalyst, the reaction did not proceed even after a prolonged reaction time (Table1, entry 1). In the presence of acidic catalysts, the reaction produced the desired product in low yields and starting materials remained even after 24 h (Table 1, entries 2-10). The model reaction was conducted in the presence of $[Et_3N–SO_3H]Cl$ under solvent-free conditions (Table 1, entries 11-14). The best result was obtained using 20 mol% of $[Et_3N–SO_3H]Cl$ at 50 °C (Table 1, entry 13). Decreasing the temperature to 30 °C (Table 1, entry 12) led to a lower yield and longer reaction time. The reaction was also examined in the presence of different quantities of $[Et_3N–SO_3H]Cl$ (Table 1, entries 13-17). Use of 20 mol% $[Et_3N–SO_3H]Cl$ was found to be optimal and afforded **6a** in 40 min in 93% yield (Entry 16).

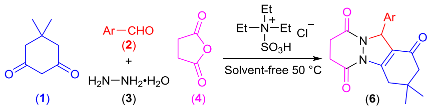


Table 1. Optimization of the reaction conditions[a]

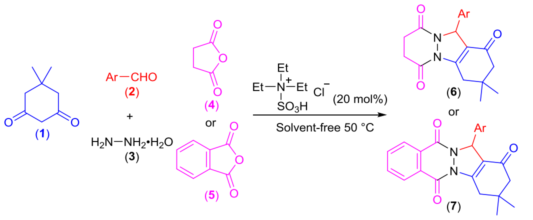
Entry	Catalyst (mol%)	Conditions	Time (h)	Yield (%)[b]
1	-	Solvent-Free (100 °C)	20	trace
2	$La(NO_3)$ (25)	EtOH (Reflux)	24	40
3	$La(NO_3)$ (25)	THF (Reflux)	24	25
4	$La(NO_3)$ (30)	Solvent-Free (100 °C)	4	30
5	$LaCl_3•7H_2O$ (20)	EtOH (Reflux)	3	35
6	$LaCl_3•7H_2O$ (20)	CH_2Cl_2 (Reflux)	24	10
7	$LaCl_3•7H_2O$ (20)	Solvent-Free (100 °C)	1	25
8	$ZnCl_2$ (30)	Solvent-Free (100 °C)	2	40
9	$ZnCl_2$ (20)	THF (Reflux)	24	25
10	$ZnCl_2$ (20)	EtOH (Reflux)	12	35
11	$[Et_3N–SO_3H]Cl$ (10)	Solvent-Free (rt)	1	40
12	$[Et_3N–SO_3H]Cl$ (20)	Solvent-Free (30 °C)	1	80
13	$[Et_3N–SO_3H]Cl$ (5)	Solvent-Free (50 °C)	1	80
14	$[Et_3N–SO_3H]Cl$ (10)	Solvent-Free (50 °C)	50 min	85
15	$[Et_3N–SO_3H]Cl$ (15)	Solvent-Free (50 °C)	45 min	90
16	$[Et_3N–SO_3H]Cl$ (20)	Solvent-Free (50 °C)	40 min	93
17	$[Et_3N–SO_3H]Cl$ (25)	Solvent-Free (50 °C)	40 min	92
18	$[Et_3N–SO_3H]Cl$ (40)	Solvent-Free (80 °C)	40 min	93

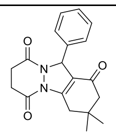
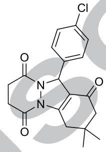
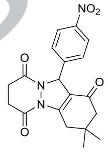
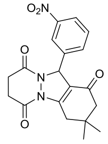
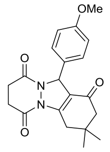
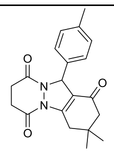
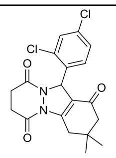
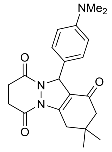
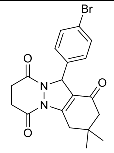
[a] Reaction conditions: **1** (1 mmol), **2a** (1 mmol), **3** (1.1 mmol) and **4** (1mmol).
[b] Isolated yield.

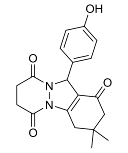
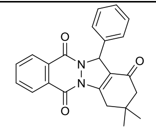
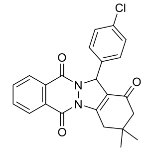
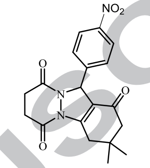
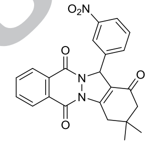
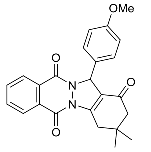
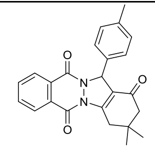
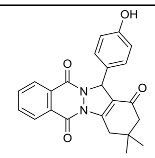
After optimization of the reaction conditions, the generality of this method was examined by the reaction of dimedone (**1**), succinic/phthalic anhydride (**4**/**5**), hydrazine hydrate (**3**) and different aromatic aldehydes (**2a-2j**) in the presence of $[Et_3N–SO_3H]Cl$ at 50 °C under solvent-free conditions (Table 2).

It was observed that aromatic aldehydes having both electron-withdrawing and electron-donating groups participated in the reaction and there was no significant difference in the reaction yield. However, electron-withdrawing substituents had shorter reaction times (Table 2, entries 2c and 2d).

Table 2. Four-component synthesis of 3,4,7,8-tetrahydro-3,3-dimethyl-11-aryl-2*H*-pyridazino[1,2-*a*]indazole-1,6,9 (11*H*)-trione and 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives[a]



Entry	Aldehyde	Anhydride	Product	Time (min)	Yield (%)[a,b]
1	PhCHO	4		40	93
2	4-ClC$_6$H$_4$CHO	4		30	93
3	4-O$_2$NC$_6$H$_4$CHO	4		25	95
4	3-O$_2$NC$_6$H$_4$CHO	4		20	87
5	4-CH$_3$OC$_6$H$_4$CHO	4		55	95
6	4-CH$_3$C$_6$H$_4$CHO	4		50	89
7	2,4-(Cl)$_2$-C$_6$H$_3$CHO	4		60	90
8	4-(CH$_3$)$_2$NC$_6$H$_4$CHO	4		15	86
9	4-BrC$_6$H$_4$CHO	4		50	90

10	4-HOC_6H_4CHO	4		35	87
11	PhCHO	5		15	87[32]
12	4-ClC_6H_4CHO	5		17	89[33]
13	4-$O_2NC_6H_4CHO$	5		10	80[32]
14	3-$O_2NC_6H_4CHO$	5		18	88[32]
15	4-$CH_3OC_6H_4CHO$	5		20	85[21]
16	4- $CH_3C_6H_4CHO$	5		25	80[34]
17	4-HOC_6H_4CHO	5		20	90[35]

[a]Reaction conditions: **1** (1 mmol), **2** (1 mmol), **3** (1.1 mmol), **4** (1 mmol), [$Et_3N–SO_3H$]Cl (20 mol%), solvent-free, 50 °C.
[b]Isolated yield.

Finally, we investigated the possibility of recycling [Et_3N–SO_3H]Cl using the model reaction forming **6a**. After reaction completion, ice cold water was added to the reaction mixture and the product was extracted with Et_2O. The aqueous layer consisting of the acidic IL, was recovered after removal of water under reduced pressure and was reused for subsequent reactions. It showed the same activity as that of the fresh catalyst without any loss of activity in terms of yield and purity. The ionic liquid could be recycled and reused in the same reaction at least four times (Table 3).

Table 3. Catalyst recycling yields[a].

No of Cycles[a]	Fresh	Run 1	Run 2	Run 3	Run 4
Yield[b]	93	93	92	91	91
Time (min)	40	40	40	40	40

[a] Reaction conditions: **1** (1 mmol), **2** (benzaldehyde, 1 mmol), **3** (1.1 mmol), **4** (1 mmol), solvent-free, 50 °C.
[b] Isolated yield.

In summary, we have synthesized 3,4,7,8-tetrahydro-3,3-dimethyl-11-phenyl-2*H*-pyridazino[1,2-*a*]indazole-1,6,9(11*H*)-trione **(6)** and 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione **(7)** derivatives by a one-pot, four-component condensation reaction of succinic/phthalic anhydride, dimedone, hydrazine hydrate, and aromatic aldehydes under solvent-free conditions using [Et_3N–SO_3H]Cl as a recoverable and highly efficient catalyst. The attractive features of this protocol are the simple procedure, clean reaction, a reusable catalyst, good yield, simple purification, as well as the ease of catalyst preparation.

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